Taiwan Food and Drug Administration

Assessment Report

Trade Name：Taflotan ophthalmic solution

Active Ingredient：Tafluprost

License Number：衛署藥輸字第 025377 號

Applicant：台灣參天製藥股份有限公司

Approval Date：100/06/09

Indication：Open angle glaucoma and ocular hypertension.

1. Background Information

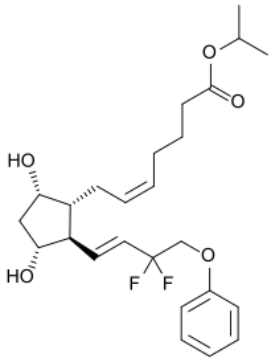
Trade Name	Taflotan ophthalmic solution
Active Ingredient(s)	Tafluprost
Applicant	台灣參天製藥股份有限公司
Dosage Form & Strengths	Ophthalmic solution, 0.015mg/ml
Indication	Open angle glaucoma and ocular hypertension
Posology	Instill 1 drop in the affected eye(s) once daily
Pharmacological Category **ATC Code**	ATC code：S01EE05

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance tafluprost, 1-methylethyl-(5Z)-7-[(1R,2R,3R,5S)-2-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxycyclopentyl]-5-heptenoate, is a colorless to light yellow viscous liquid. The empirical formula is $C_{25}H_{34}F_2O_5$ and the molecular weight is 452.53. It is very soluble in ethanol, but insoluble in water.



It contains four stereo centers, and is synthesized as the single stereoisomer. The following physicochemical properties were investigated: physical description, hygroscopicity, melting point and optical rotation. The structure of tafluprost is identified by UV, IR, MS, NMR and elemental analysis. The sponsor has submitted adequate information on characterization of the drug substance.

The proposed specifications include tests for appearance, color and clarity of solution, identification, assay, structural related substances, heavy metals, residue on ignition and residual solvents. All control tests and specification are considered acceptable and established according to the synthetic process, ICHQ6A Guidance and historical batch results. Batch analyses were presented and the acceptance criteria were met.

2.1.2 Drug product

The drug product Taflotan® ophthalmic solution (0.015 mg/mL) is presented as solution. The excipients complied with pharmacopoeia standard are compatible with tafluprost. The commercial processes have involved the preparation of drug solution, sterile filtration, filling, plugging and capping, packaging and labeling.

Adequate release and shelf-life specification have been presented for the Taflotan® ophthalmic solution. The tests include description, identification, assay, osmolar ratio, pH, insoluble particulate matter, foreign insoluble matter, related substances and sterility. The specification is deemed satisfactory in line with pharmacopoeia and/or ICH Guidance. Analytical methods have been well described and validated. Batch analysis results are all remained within the specification.

Stability studies under long-term, intermediate and accelerated conditions (25°C/40% RH, 30°C/75% RH and 40°C/< 25% RH) have been carried out on three commercial batches and manufactured at the same site proposed for marketing. Up to 36 months of long-term, 12 months of intermediate and 6 months of accelerated stability data are submitted. The available results showed that no significant changes were observed for any parameter tested at both conditions. The shelf life of Taflotan® ophthalmic solution is 36 months under the storage condition of 25°C.

Information on the active substance and finished product have been presented and regarded as appropriate. A consistent and reproducible product should be yielded.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Pharmacology data showed tafluprost has strong ocular hypotensive effect, not only in the ocular hypertension eyes, but also in the ocular normotensive eyes. In safety pharmacology, tafluprost showed weak effects on cardiovascular system and uterine motility, however these effects were considered to be non-specific and similar to those of PGF2α.

2.2.2 Toxicological Studies

In toxicology, repeated intravenous administration with tafluprost resulted in adverse effects including hyperostosis and myelofibrosis in the bone marrow and increased hemopoiesis in the spleen and liver (rats) and transient miosis, vomiting, loose stool, increased heart rate, and increased blood pressure (dogs). In ocular administration route, external changes (sunken upper eyelid, iris color change) were observed in monkeys.

Safety margins of tafluprost were 36 folds and 216 folds in dogs and monkeys, respectively. Although the safety margin is not set in rats, these changes caused by tafluprost were concluded to be pharmacological effects of prostaglandin analogues or secondary effects specific to rats. Tafluprost did not show genotoxicity or carcinogenicity potential. In reproductive toxicology, an increase of post-implantation loss, abortion and fetal malformation were observed. The findings raised from these toxicity studies of tafluprost are generally those caused by other prostaglandin analogues or PGF2α as well, and therefore, they can be considered class effects of prostaglandins.

In conclusion, the sponsor provides adequate preclinical pharmacology and toxicology information to support a favorable efficacy and safety of Taflotan® for the treatment of glaucoma and ocular hypertension in clinical. It is recommended that Taflotan® should be used during pregnancy only if clearly needed. From PharmTox view, this NDA is recommendable.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The active ingredient of Taflotan® is tafluprost with 0.0015%. Tafluprost was absorbed quickly into systemic circulation following ocular administration but in extremely low concentration. The tafluprost and tafluprost acid concentrations for most of blood samples following single (0.0001%, 0.0005%, 0.0025% and 0.005%) and multiple (0.0025% and 0.005%) dosing were lower than the lower limit of quantitation (LOQ of tafluprost and tafluprost acid was 0.2 ng/ml and 0.1 ng/ml, respectively). After administration of single dose of 0.005% 3H-tafluprost to the eyes of cynomolgus monkeys, it penetrated the cornea which served as a depot and was slowly released into the anterior parts of the eye. Peak radio-related concentrations in ocular tissues were observed at 5 to 15 minutes postdose in cornea and conjunctiva, 2 hours postdose in aqueous humor, iris, iris-ciliary body and lens. Great amount of tafluprost-related radioactivity following ocular administration was observed in the gastrointestinal tract. Tafluprost and its metabolites did not cross the blood-brain barrier of rat, but secreted into lactating milk and transferred to fetus through placenta. Avoid use of tafluprost was recommended to pregnant women and nursing mother. Tafluprost is rapidly hydrolyzed to tafluprost acid by carboxylesterase. Other enzymes involved in the multiple pathways subsequently were unidentified. Most of the radioactivity was excreted by 48 hours post dose after ocular administration of ^{3}H-talfuprost (1 μg/eye) in monkey.

2.3.2 Interaction Studies

Due to the low systemic exposure of tafluprost and tafluprost acid, the lack of drug-drug interaction information would be acceptable.

2.3.3 Special Populations

Due to the low systemic exposure of tafluprost and tafluprost acid, the lack of special population information would be acceptable.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The efficacy of Taflotan 0.0015% indicated for the treatment of glaucoma and ocular hypertension was evaluated in 3 Phase II/III studies conducted in Japan (Studies [850-202]), [850-303] and [850-304]) as well as 3 Phase III studies conducted in US or European countries (Studies [74458], [15003] and [74460]). The key differences between these studies are: a longer treatment duration (6 weeks - 24 months) with an evening dosing time (8 PM) was used in US/European studies, while a short-term duration (4 weeks) with a morning dosing time (10 AM) was used in studies conducted in Japan. The efficacy findings of the six studies are summarized below:

- ***Study [850-202]:***

Study [850-202] was a Phase II, double-blind, dose-range study comparing 0.0003%, 0.0015%, and 0.0025% Taflotan with placebo in patients with primary open-angle glaucoma or ocular hypertension. The mean decrease from baseline in IOP at Week 4 (LOCF) (the primary endpoint) for all randomized population was 3.1 mmHg in the placebo group, 5.1 mmHg in the Taflotan 0.0003% group, 5.1 mmHg in the Taflotan 0.0015% group, and 6.2 mmHg in the Taflotan 0.0025% group. Because the normality assumption of the primary endpoint was not satisfied, a between-group comparison using Wilcoxon rank sum test was thus conducted. The results showed a statistically significant difference between each Taflotan group and placebo using Bonferroni adjustment (p-values = 0.0157, 0.0054 and 0.0015 for 0.0003%, 0.0015%, and 0.0025% Taflotan, respectively).

- ***Study [850-303]:***

Study [850-303] was a Phase III, randomized, active-controlled study in 109 patients with primary open-angle glaucoma or ocular hypertension. For the PPS at Week 4 (LOCF), the decrease in IOP was 6.6 mmHg in the Taflotan 0.0015% group compared to 6.2 mmHg in the Latanoprost 0.005% group; the 2-sided 95% CI for the treatment difference (Taflotan minus Latanoprost) was -1.42 to 0.60 mmHg. The upper 95% CI was less than pre-defined margin of 2 mmHg. Similar results were obtained for both the FAS and all randomized populations. However, the study was conducted in a single-blind (investigator-blind) fashion and the blinding scheme used in this study was difficult to keep investigator blinded. The potential bias will be a concern.

- ***Study [850-304]:***

Study [850-304] was a Phase III, randomized, double-blind, placebo-controlled study in 94 patients with normal tension glaucoma. The primary endpoint was the mean reduction of IOP from baseline to end of treatment in the FAS. The results showed that the IOP lowering effect was statistically significantly greater in the Taflotan 0.0015% group compared with placebo (4 mmHg vs. 1.4 mmHg; $p < 0.001$). Analyses of the secondary efficacy endpoints (e.g., IOP lowering effects at Week 2 and Week 4; and percent change in IOP from baseline at Week 2 and Week 4, etc) further confirmed the superiority of Taflotan 0.0015% group over placebo.

- ***Study [74458]:***

Study [74458] was a Phase III, randomized, double-masked, active-controlled study to assess the non-inferiority of Taflotan 0.0015% qd to Latanoprost 0.005% qd in patients with primary open-angle glaucoma or ocular hypertension. The primary efficacy endpoint was the change from baseline in overall diurnal IOP at 6 months. In the ITT population, the estimated overall treatment difference (Taflotan – Latanoprost) at 6 months was 1.44 mmHg (upper 95% CI: 1.84 mmHg) using repeated measurements analysis of covariance (RM ANCOVA). The upper 95% CIs wase above the pre-defined non-inferiority margin of 1.5 mmHg, thus results from this study failed to show the non-inferiority of Taflotan 0.0015% qd to Latanoprost 0.005% qd in IOP lowering effect.

- ***Study [15003]:***

Study [15003] was a Phase III, randomized, double-masked, active-controlled study to evaluate the non-inferiority of Taflotan 0.0015% qd to Timolol 0.5% bid in patients with primary open-angle glaucoma or ocular hypertension. The primary efficacy endpoint was the change from baseline in overall diurnal IOP at 6 months. In the ITT population, the estimated overall treatment difference (Taflotan – Timolol) at 6 months was -0.279 mmHg (upper 95% CI: 0.214 mmHg) using RM ANCOVA. Similar results were observed from the PP population: the estimated overall treatment difference (Taflotan – Timolol) at 6 months was -0.188 mmHg (upper 95% CI: 0.297 mmHg) using RM ANCOVA. Since the upper 95% CIs were all below the pre-defined margin of 1.5 mmHg, the non-inferiority of Taflotan 0.0015% qd to Timolol 0.5% bid in IOP lowering effect was demonstrated from this study.

- ***Study [74460]:***

Study [74460] was a Phase III, randomized, double-masked, vehicle-controlled study to assess the efficacy of Taflotan 0.0015% qd as adjunctive therapy with Timolol 0.5% bid in patients who were not partially controlled with Timolol treatment. The primary efficacy endpoint was change from baseline in overall diurnal IOP at 6 weeks. In the ITT population, the estimated overall treatment difference (Taflotan – vehicle) at 6 weeks was -1.49 mmHg (upper 95% CI: -0.66 mmHg) using RM ANCOVA. The analyses confirmed the superiority of Taflotan 0.0015% qd over vehicle after 6 weeks of treatment.

In summary, the two adequate designed, well-controlled studies (Study [850-202] and Study [15003]) provide sufficient evidence to support the efficacy of Taflotan 0.0015% for the claimed indication. Results from the remaining four studies ([850-303], [850-304], [74458] and [74460]) further support the efficacy of Taflotan 0.0015% for the treatment of patients with primary open-angle glaucoma or ocular hypertension.

2.4.2 Safety Results

Major adverse events include conjunctival hyperemia, eye pruritus, growth of eyelashes, eye irritation, eye pain, foreign body sensation of eyes, iridal pigmentation, pigmentation of eyelid and punctate keratitis. Conjunctival hyperemia, iridal pigmentation, pigmentation of eyelid and growth of eyelashes are class effects of prostaglandin analog.

2.5 Bridging Study Evaluation

In addition to the low systemic exposure of tafluprost and tafluprost acid, the human PK information of Taflotan® was obtained from Japanese. The concern of ethnic sensitivity of Taflotan® would be minimal from pharmacokinetic perspective.

The sponsor provided 3 Japanese studies; Studies [850-202], [850-303] and [850-304]. Study [850-202] is a Phase II, double-blind, dose-range study comparing 0.0003%, 0.0015%, and 0.0025% Taflotan with placebo in patients with primary open-angle glaucoma or ocular hypertension. Study [850-303] is a Phase III, randomized, active-controlled study in 109 patients with primary open-angle glaucoma or ocular hypertension. Study [850-304] is a Phase III, randomized, double-blind, placebo-controlled study in 94 patients with normal tension glaucoma.

In Study [850-303], Taflotan 0.0015% group was non-inferior to Latanoprost 0.005%

group at Week 4. In Study [850-304], Taflotan 0.0015% group was superior to placebo at Week 4.

2.6 Conclusion

For the indication of open-angle glaucoma, the efficacy of Taflotan 0.0015% was supported by one phase II study and 6 phase III studies. Major adverse events include conjunctival hyperemia, eye pruritus, growth of eyelashes, eye irritation, eye pain, foreign body sensation of eyes, iridal pigmentation, pigmentation of eyelid and punctate keratitis. The benefit outweighs the risk.

3. Post-Marketing Requirements

Routine post-marketing surveillance as required by Department of Health is adequate. No additional REMS is required.